REMARKS

The following claims are pending in the application:	1 – 34
The following claims have been amended:	1, 4, 5, 6, 7, 11 and 13
The following claims have been deleted or withdrawn:	17-34
The following claims have been added:	N/A

As a result of the foregoing Amendment, the following claims remain pending in the application: 1 – 16.

Election/Restriction Requirement

Applicants have elected to prosecute the claims drawn to a method of treating diabetes in humans, which are covered by claims 1 – 16.

The Objections to the Specification

The Examiner has objected to the specification owing to the use of certain trademarks. Applicants have supplemented the specification to describe generically the nature of Sustacal, which is known in the art.

Applicants respectfully submit that the trade name ALHYDROGEL-DIAMYD is already described as an alum-formulated rhGAD65 in paragraph [0095]. Other forms of this same drug are referred to elsewhere in the specification simply as DIAMYD or the DIAMYD drug. See e.g., paragraph [0102].

Applicants have used the registered trademark symbol to be sure proprietary rights in others' marks are protected.

Accordingly, Applicants respectfully submit that the specification is clarified in respect to the use of trademarks and trade names.

Applicants have also added the proper serial number and filing date of the provisional application in support of the priority claim herein.

The Provisional Double-Patenting Rejection

Applicants will submit a terminal disclaimer in the event the subject application is otherwise in condition for allowance.

The Rejection under 35 USC 112

The Examiner has rejected claims 1 – 7 under 35 USC 112, second paragraph, owing to the presence of the term "an effective time." Applicants respectfully submit that this would be implied in any treatment and, accordingly, have simply removed this term such that the claims are directed to a functionally effective treatment method.

The Examiner has rejected claims 1, 4, 6, 8, 11 and 13 under 35 USC 112, second paragraph, because the claims recite a dosage "at a level of at least 20 micrograms." Applicants have amended these claims to clarify the intended dosage level. Applicants respectfully submit that dosage range may properly be expressed as a range bearing only a lower limit without being objectionable under 35 USC 112, second paragraph. Applicants have also amended these claims to remove use of the term "level" so that there is no confusion but that reference is only intended to the dosage magnitude, and that no measurement determination and correlation step is required. Applicants have

also amended the claims to more clearly specify that the given dosage magnitude of the booster is that of the booster alone.

In this same regard, Applicants respectfully submit that , while the measurement of insulin might be necessary to determine whether a given method meets the functional language of the method, the method of the present invention would be practiced even without the practitioner actually measuring insulin. By this reasoning (if the Examiner required the inclusion of a measurement step), anyone could practice the claimed therapeutic method so long as they did not measure the level of insulin production) Accordingly, Applicants respectfully submit the failure to recite an affirmative measurement step does not render the claims non-compliant with Section 112, second paragraph.

The Rejection under 35 USC 102

The Examiner has rejected claims 1-16 as allegedly anticipated by a number of references.

As to the Lernmark et al. reference, this reference reports Applicants' own invention and thus is not prior art under 35 USC 102(a).

The other prior art references do not teach or suggest that insulin production may be increased in humans as is brought about unexpectedly in the present invention.

The cited references do not teach or suggest that an actual increase in insulin production (as opposed to merely a stabilization in beta cell function). The US prior art as referenced in the Office Action offer do not teach or suggest that the level of insulin can actually be increased in humans using the claimed method.

While the prior art references offer some speculation that GAD65-alum should work in humans, there existed in the prior art an equal amount of teachings that warned that GAD65-administration could precipitate rather than ameliorate disease and some argued that GAD65 would probably not work in humans whereas other antigens were more likely to, if at all. This is especially true with respect to any role GAD65 might play in T1D disease.

The human immune system is unique and complex and Applicants respectfully submit that results drawn from theoretical contemplations or animal or *in vitro* studies cannot be extrapolated to make efficacy of GAD65-alum in humans obvious.

At the time of the advent of the present invention, the use of State of prior art. Nobody had tried GAD. intervention in humans. Nor had any other autoimmune disease been ameliorated in humans with autoantigen-specific therapy. In fact it was believed by most that insulin was the most important autoantigen and immunomodulation with insulin was initiated with the US Diabetes Prevention Trial 1 (DPT1) in 330 subjects with high risk to develop type 1 diabetes. The study came out negative. Diabetes had at the time been prevented in the NOD mouse, the animal model for human type 1 diabetes, with approximately 100 different therapeutic strategies including with insulin and GAD.

As to the relevant degree of predictability, the reactions of the human immune system to antigen-specific therapy is totally unpredictable. For example, although a small pilot study showed that insulin may work as an immunomodulatro to prevent or delay diabetes, the DPT 1 trial using insulin came out with negative results. Another example is the Neurocrine clinical studies where a peptide from Myelin Basic Protein, a

major autoantigen in multiple sclerosis (MS), was used in an effort to ameliorate the disease. This clinical study was abruptly stopped as some patients suffered from precipitation of disease. Animal studies have indicated that different GAD65-peptides can both protect and precipitate disease. GAD65 had precipitated disease in at least one animal study. In short, nobody could predict with any reliability the outcome of the study resulting in the present invention.

In accordance with the present invention, a phase II study in LADA patients was needed to discover that two subcutaneous injections of each between 10 - 50 micrograms full-length GAD65 formulated in alum had a positive long-term impact on LADA patients diagnosed with the disease within 5 years.

As to the cited references in particular, the Kaufman reference (US Pat 6,022,697) does not teach or suggest stimulating the production of insulin to a level above that existing prior to treatment, as in the present invention. Kaufman merely speculates that administration of GAD65-antigen could slow down the autoimmune destruction of beta cells in pre-diabetes individuals or in type 1 diabetes patients. Even this effect would not allow insulin production to increase, such as through treating patients with Latent Autoimmune Diabetes in the Adult (LADA).

In addition, Kaufman speculates that evaluation of the efficacy of GAD65-treatment in man can be made by measuring the GAD65-antigen specific Th2/Th1 quotient. The present invention, which is reduced to practice, discloses the use of relative increase of CD4+CD25+ regulatory T cells which is different.

The Kaufman reference merely speculates that alum is a suitable adjuvant to use when inducing tolerance to GAD65 in type 1 diabetes. Immunomodulation is a very

complex task and the immune system is far from understood. For example, was it not known in the art, and it is still under debate, whether induction of GAD65-antibodies may aggravate or ameliorate type 1 diabetes. It has been shown that different classes of IgG antibodies are associated with different aggressivity in autoimmune disease and that therefore the risk existed that GAD65-immunization using alum as an adjuvant would induce an antigen class switch to a more aggressive antigen. In addition, it was totally unknown if immunization with GAD65-alum might induce antigen epitope spreading that is if induced antibodies would be directed to new targets. The study evidencing the efficacy of the present invention showed that two subcutaneous injections of 20 microgram GAD65 in alum only marginally increased the GAD65-antibody titers, which was unexpected (and beneficial because high antibody titers are associated with fast precipitation of type 1 diabetes) and that the patients fared better, i.e. the formulation worked, meaning alum as an adjuvant in modulating antigen response in an autoimmune disease worked and that the claims of the present invention were reduced to practice.

Likewise, none of the other cited references, such as the Tobin and Baekkeskov references, teach or suggest the present invention for the same reasons.

With regard to the Harrison reference, this reference discloses the use of peptides rather than full length proteins. It has been shown that some peptides precipitate disease whereas other protect. This may vary with an individual's genetic disposition (HLA-antigens), and thus little guidance respecting the present invention can be gained from this teaching.

CONCLUSION

In view of the foregoing amendment and accompanying remarks, the Applicants respectfully submit that the present application is properly in condition for allowance and may be passed to issuance upon payment of the appropriate fees.

Telephone inquiry to the undersigned in order to clarify or otherwise expedite prosecution of the subject application is respectfully encouraged.

Respectfully submitted,

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